Comparison of uninterrupted warfarin and bridging therapy using low-molecular weight heparin with respect to the severity of bleeding after dental extractions in patients with prosthetic valves

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Abstract

Objective: The management of anticoagulated patients with warfarin during dental extraction is an intricate issue. We carefully designed the current study so that the amount of bleeding was measured with objective methods and the data from the same patient in different dental extraction appointments could be compared, eliminating the bleeding diathesis differences of patients.

Methods: This prospective and controlled study was conducted in 36 adult patients with prosthetic valve requiring multiple tooth extractions. The first dental extraction was performed without the discontinuation of warfarin therapy, and the second procedure was performed with a discontinuation of warfarin and bridging with low-molecular weight heparin (LMWH). The two dental extraction protocols in the same patient group were compared. The total amount of bleeding was calculated as the difference between the weights of gauze swabs used before and after the tamponade; the number of gauze swabs used for bleeding control in the first 48 h was recorded.

Result: The median number of used gauze swabs was 2.5 (IQR: 1–5) and 3.0 (IQR: 2–7) in the first and second dental extraction procedures, respectively. The median bleeding time was 50.0 (IQR: 20–100) in the first procedure compared with 60.0 (IQR: 40–140) min in the second procedure. The mean amounts of bleeding were 2194±1418 mg in the first dental extraction procedure and 2950±1694 mg in the second dental extraction procedure. The median number of used gauze swabs, the median bleeding time, and the mean amount of bleeding were statistically higher in the second dental extraction procedure ($p<0.001$).

Conclusion: Continued warfarin treatment at the time of dental extractions reduces the total amount of bleeding compared with bridging therapy in patients with prosthetic valves. *(Anatol J Cardiol 2016; 16: 467-73)*

Keywords: dental extraction, prosthetic valve, bridging therapy

Introduction

The number of anticoagulated patients has been growing constantly. Each year, 10% of these patients require a short-term interruption of their anticoagulation therapy to perform an invasive procedure. Defining the most appropriate management strategy for these patients requires an assessment of the periprocedural risk of thromboembolism and major hemorrhage. Bridging therapy is a recent term used to describe the application of a parenteral, short-acting anticoagulant during the interruption of warfarin (1). However, there are a number of potential drawbacks to bridging with heparin in the perioperative period. This protocol is time and resource consuming and increases the costs. Bridging with heparin also involves a short period of restored coagulation status, perhaps even hypercoagulability related to the prothrombotic state of surgery, with an associated risk of thromboembolism. Bridging anticoagulation refers to using a short-acting anticoagulant, usually low-molecular weight heparin (LMWH), which is administered by subcutaneous injection for 10–12 days around the time of the procedure during warfarin interruption. However, a residual anticoagulant effect has been demonstrated in a number of patients after 24 h. Previous studies have confirmed that heparin bridging may be associated with an increased risk of bleeding complications (2, 3).

The decision on how to manage patients on warfarin therapy before dental extraction is determined according to

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the international normalized ratio (INR) and the thromboembolic risk of the given patient. In patients at moderate-to-high risk (≥5% per year) for thromboembolic events, the commonly used protocols are tooth extraction with or without an interruption of warfarin and use of bridging anticoagulation with LMWH or unfractionated heparin (UFH) (4-6).

Several prospective controlled studies have compared the outcomes of different protocols for dental extractions (7-16). These studies determined bleeding complications by subjective measurement methods, which are based on patients' feedback or clinicians' observations. However, in these studies, the amount of bleeding was not measured with objective methods and the variability of the patients with respect to the bleeding diathesis was not taken into consideration.

The aim of this study was to compare uninterrupted oral anticoagulation therapy (OAT) (group A) and bridging therapy with LMWH (enoxaparin sodium, Clexane, Sanofi-Aventis) (group B) with respect to the risk of hemorrhage and thromboembolic complications at the time of dental extractions in patients with prosthetic heart valves. We think that there are two aspects that increase the importance of our study compared with previous reports related to this issue. First, we quantitatively measured the amount of bleeding, in spite of using some qualitative methods. Second, the two treatment strategies were compared in different dental extraction appointments for the same patient. Thus, limitation of a possible variability arising between the two treatment groups with respect to the bleeding diathesis was eliminated.

Methods

This clinical, prospective, and controlled study was conducted in 36 adult patients with prosthetic valves requiring dental extractions without a need for a mucoperiosteal flap raise and who were admitted to the department of dentistry. All the patients had prosthetic heart valves and an annual predicted risk of thromboembolism of at least 5% (4, 5). Patients with a history of chronic renal or liver disease or who were on drugs other than warfarin that could affect liver function or hemostasis were excluded. The study was approved by the local Ethics Committee. All the patients had given their written informed consents.

More than one tooth extraction was required in all patients. The teeth were grouped as molar, bicuspid or cuspid, and incisor according to the Universal Tooth Numbering System. Furthermore, the incisors were subgrouped as maxillary or mandibular. To eliminate the potential influence of structural differences of the teeth extracted on bleeding, teeth from the same dental groups were selected in both separate sessions. Patients not meeting these selection criteria were excluded. In each patient, the first dental extraction was performed without a discontinuation of warfarin therapy (with a mean INR of 2.5±0.3) (group A), while the second dental extraction was performed with bridging using LMWH (enoxaparin sodium, Clexane, Sanofi-Aventis) after the discontinuation of warfarin (group B). The two dental extraction protocols performed at separate times on the same patient were compared. At the first visit, a full medical history was taken; radiographic and clinical examinations were performed. A preoperative INR was measured for all the patients. If a patient's INR was above 4.0 on the day of the operation, extraction was postponed until the INR level was below 4.0. The dental extractions were performed under local anesthesia using 2% prilocaine without adrenaline (Priloc, VEM Ilaç San Lim Şti, Ankara, Turkey). Before extraction, the oral cavity was protected from salivary secretions by placing sponge gauze pads on the orifices of the bilateral parotid, submandibular, and sublingual gland ducts and by continuous suctioning using surgical aspirators. All the extractions were performed by the same surgeon using laxators and forceps. Extractions that were complicated during the operation and required a flap elevation were excluded from the study. After the completion of the extraction procedure, tamponades were used to stop bleeding from the extraction sockets, and these were subsequently changed for gauze swabs after 20 min. Each gauze swab was pressed gently over the extraction socket and changed for a new swab once it had absorbed a sufficient amount of blood. The weights of gauze swabs used before and after the tamponade were measured using a fine electronic weight measurement device (Densi HZY 1000, China). The weight differences between the pre- and post-tamponade gauzes were interpreted as the amount of bleeding (AOB; mg). After 20 min of tamponade, each extraction socket was packed with oxycellulose dressing and sutured with 3.0 silk sutures. A new gauze swab was placed over the surgical area, and the patient was instructed to bite on it for 1 h. Patients were given additional gauze swabs to be used if bleeding continued and were advised to admit themselves to the emergency department in the event of severe bleeding. They were asked to count the number of extra gauze swabs used for bleeding control during the first 48 h. Paracetamol was prescribed for pain control. No postoperative antibiotics or mouthwashes were prescribed. All the patients were clinically examined and questioned about the number of gauze pads used for bleeding control. The sutures were removed 48 h after extraction. Patients were recalled at 10 days postoperatively for the evaluation of the wound healing. The second dental extraction procedure was performed at least 15 days after the first procedure. Patients in the heparin-bridging group discontinued warfarin therapy 5 days before the procedure and started receiving full therapeutic doses of LMWH. For patients receiving bridging therapy with LMWH, the final dose was administered during

the evening before the procedure (i.e., >12 h before the procedure). The injection of heparin was reinitiated 24 h after the invasive procedure and was continued until a therapeutic INR was achieved. The number of tooth roots removed during tooth extraction was identical between the two procedures, and only one tooth was extracted from each patient in each session.

Statistical analysis

The number of patients included in this study was based on the average amount of bleeding obtained from previous studies. We calculated that at least 20 patients should be included in each group to detect a difference of 30% between the two groups, with a value of α of 0.05 and β of 0.20. The normality of distribution of the continuous variables was tested by the Kolmogorov–Smirnov test. Continuous variables were expressed as the mean ± standard deviation if normally distributed. Non-normal distributed continuous data were expressed as the median (interquartile range). Each categorical variable was expressed as the number and percentage of patients. The group means of the continuous variables with a normal distribution were compared using the paired samples test, while the group means of the non-normal distributed continuous variables were compared using the Wilcoxon test. The McNemar test was used to compare the categorical variables. The correlation between the INR values and the amount of bleeding in the patients under warfarin therapy was performed by the Pearson test. Two tailed p values of less than 0.05 were considered to demonstrate a statistical significance. All the analyses were performed using SPSS 15 (SPSS, Inc., Chicago, IL, USA).

Results

Seventy-two tooth extractions were performed in 36 patients (17 male, 19 female) with prosthetic heart valves. The mean age of the patients was 46.8±11.4 years (range: 28–72 years). The baseline characteristics of the patients are shown in Table 1. The mean INR were 2.5±0.3 and 1.1±0.1 in the group A dental extraction procedure and the group B dental extraction procedure, respectively (Table 2). The median number of used gauze swabs was 2.5 (IQR: 1–5) in the group A dental extraction procedure compared with 3.0 (IQR: 2–7) in the group B procedure. The median number of used gauze swabs was higher in the group B dental extraction procedure (p<0.001). The median bleeding time was 50.0 (IQR: 20–100) min in the group A dental extraction procedure and 60.0 (IQR: 40–140) min in the group B procedure (p<0.001). The median bleeding time was significantly higher in the group B dental extraction procedure (p<0.001). The mean AOBs were 2194±1418 mg and 2950±1694 mg in the group A dental extraction procedure and the group B dental extraction procedure, respectively (p<0.001) (Table 2). Figure 1 shows the correlation between the amount of bleeding and the bleeding time. None of the participants in either

Table 1. Characteristics of the patients at baseline*

Characteristic	Patient (n=36)
Age, year	46.8±11.4
Female sex, n (%)	19 (52.7%)
Body mass index	29.8±6.1
The type of valve replacement	
1. Mechanical mitral-valve replacement	23 (63.8%)
2. Mechanical aortic valve replacement	9 (25%)
3. A patient could have more than one valve	4 (11.1%)
Medical history, n (%)	
Rheumatic heart disease	23 (63.8%)
Embolic transient ischemic attack	2 (5.5%)
Hypertension	21 (58.3%)
Diabetes mellitus	5 (13.8%)
Cardiomyopathy	3 (8.3%)
Coronary artery disease	9 (25%)
Atrial fibrillation or atrial flutter	12 (33.3%)
Medications, n (%)	
1. Aspirin	8 (22.2%)
2. Statin	9 (25%)
3. Angiotensin-converting–enzyme inhibitor	7 (19.4%)
4. Angiotensin-receptor blocker	13 (36.1)
5. Amiodarone	1 (2.7%)
6. Beta-blocker	13 (36.1%)
7. Loop diuretic	5 (13.8%)
8. Calcium channel blocker	6 (16.6%)

*Plus–minus values are mean±SD

Table 2. Results of bleeding complications using different perioperative anticoagulant strategies. *

	Uninterrupted Warfarin therapy n=36	Bridge therapy with LMVH n=36	*P*
Amount of bleeding, mg	2194±1418	2950±1694	<0.001*
Bleeding time, min	50.0 (20, 100)	60.0 (40, 140)	<0.001†
Suture need, n (%)	1 (0.02%)	4(0.1%)	0.25‡
Number of used extra gauze swabs	2.5 (1, 5)	3.0 (2, 7)	<0.001†
Mean INR	2.5±0.3	1.1±0.1	<0.001*

*Values are median (25th, 75th percentiles), n (%) or mean ± SD. The median number of used extra gauze swabs, the median bleeding time and the mean AOBs were all higher in the second dental extraction procedure group (P<0.001). *Paired samples test, †Wilcoxon test, ‡McNemar test.

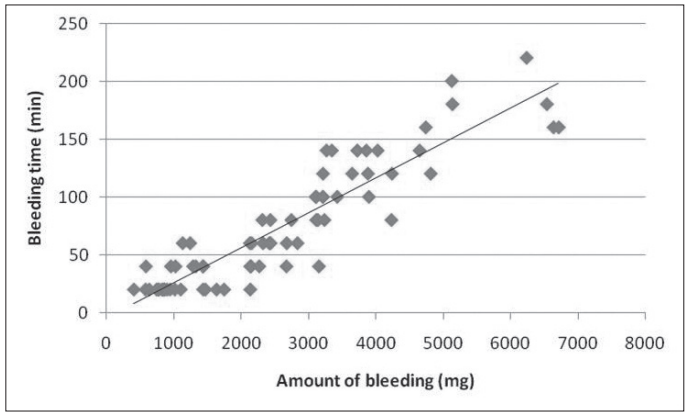

Figure 1. Correlation between the amount of bleeding and the bleeding time

group experienced thromboembolic complications. The numbers of extracted teeth are reported according to the Universal Tooth Numbering System (Table 3).

Discussion

This study showed that uninterrupted warfarin treatment at the time of tooth extractions reduces the total amount of bleeding compared with bridging therapy with LMWH in patients with prosthetic heart valves. In contrast to some previous studies, comparison of the two therapeutic strategies in the same patients eliminates all the confounders regarding bleeding diathesis.

The periprocedural management of anticoagulated patients with warfarin during dental extraction is a complicated issue. Approaches in caring for anticoagulated patients during dental extractions vary from tooth extraction without the interruption of warfarin therapy or the interruption of warfarin and use of bridging anticoagulation with LMWH or UFH. Previous studies did not show any cases of severe postextractional bleeding in patients who continued warfarin; however, several cases of fatal thromboembolic complications have been reported after stopping warfarin before a dental extraction (2-6).

The administration of epinephrine is not an absolute contraindication for patients with cardiovascular disease, but a 3% prilocaine solution without epinephrine was used to eliminate the vasoconstrictive effects of epinephrine on the extraction sockets, which may deteriorate standardization of the procedure. To achieve standardization, extractions requiring flap elevations were excluded from the study. Pressure with gauze swabs on the extraction socket is a standard practice for providing effective hemostasis, and the amount of blood absorbed by the gauze swab is a good indicator of bleeding (7). The amount of immediate postoperative bleeding was measured by the weights of the gauze swabs before and after use within a certain period (20 min) and early postoperative bleeding was determined based on the counting the number of extra gauze swabs used within 48 h after extraction. A fine electronic balance was used for determination of the AOB, which interpreted the AOB as the quantity of blood loss (mg). This technique, also used in the

Table 3. Distribution of extracted teeth for each group*

Patient number	Uninterrupted Warfarin therapy (Group A)	Bridge therapy with LMVH (Group B)
1	18	32
2	15	17
3	10	11
4	31	32
5	13	12
6	17	1
7	27	26
8	20	21
9	18	16
10	19	18
11	11	10
12	14	31
13	31	30
14	28	29
15	3	2
16	26	25
17	31	19
18	7	6
19	5	13
20	19	16
21	15	16
22	31	32
23	4	5
24	29	28
25	18	17
26	2	1
27	30	16
28	22	23
29	2	1
30	3	8
31	11	10
32	15	14
33	18	17
34	14	15
35	3	2
36	2	1

*Teeth were coded according to the Universal Tooth Numbering System; 17 teeth were extracted from the mandible and 19 from the maxilla in group A. 16 teeth were extracted from the mandible and 20 from the maxilla in group B.

study of Karslı et al. (8), provided quantitative data for comparison of the postoperative AOB in patients on warfarin.

The contemporary literature contains strong evidence of safe methods for dental extractions in patients with INR levels lower than 4.0, in which hemostasis is provided by local measures. Devani et al. (9) designed a clinical study to compare two approaches in the management of anticoagulated patients undergoing dental extractions. A control group of 32 patients had their warfarin treatment stopped for 2–3 days prior to having dental extractions, resulting in a reduction in the average preoperative INR from 2.6–1.6. Their study group of 33 patients did not have their anticoagulant treatment altered before the extractions, and had an average preoperative INR of 2.7. None of the patients had any immediate postoperative bleeding, and only 1 patient from each group had mild delayed hemorrhage, which was easily controlled with local measures. Bajkin et al. (10) evaluated postoperative bleeding and thromboembolic complications during dental extractions in anticoagulated patients using two different protocols. In total, 214 anticoagulated patients in need of simple dental extractions were randomized into 2 groups. Group A consisted of 109 patients on continuous OAT, with a mean INR of 2.45±0.54. Group B consisted of 105 patients on bridging therapy with LMWH (nadroparin calcium, Fraxipoarine Sanofi, Winthrop, France), with a mean INR of 1.26±0.11 on the day of the procedure. Eight (7.34%) patients in group A and 5 (4.76%) patients in group B manifested postextractional bleeding, without statistical significance. All the cases of hemorrhage were mild and easily controlled using local hemostatic measures. Bacci et al. (11) performed a large, multicenter, prospective, case-control study to further assess the incidence of bleeding complications after dental extraction in patients taking OAT. Four hundred and fifty-one patients being treated with warfarin who required dental extraction were compared with a control group of 449 non-anticoagulated subjects undergoing the same procedure. In the warfarin treated group, the oral anticoagulant regimen was maintained unchanged, such that the patients had an INR ranging between 1.8 and 4. Seven bleeding complications occurred in the OAT group and four in the control group; the difference in the number of bleeding events between the two groups was not statistically significant (OR=1.754; 95% CI 0.510–6.034; p=0.3727). Evans et al. (12) investigated whether patients who were taking warfarin and had an INR within the normal therapeutic range required cessation of their anticoagulation drugs before dental extractions. Of 109 patients who completed the trial, 52 were allocated to the control group (warfarin stopped 2 days before extraction) and 57 patients were allocated to the intervention group (warfarin continued). The incidence of bleeding complications in the intervention group was higher (15/57, 26%) than in the control group (7/52, 14%), but this difference was not significant. Salam et al. (13) assessed the incidence of bleeding after dental extractions in subjects taking warfarin continuously before and after extractions whose INR was below 4.0 at the time of extraction. A total of 58 women and 92 men were included in the study. The mean INR was 2.5±0.56, although most patients had an INR of less than 2.5 (n=101). Ten patients (7%) bled after extraction, enough to require a return to hospital. Five patients out of 101 with an INR ≤2.5, and 5 with an INR >2.5 out of 49 bled after extraction (p=0.29). Blinder et al. (14) evaluated the incidence of postoperative bleeding in patients treated with oral anticoagulant medication who underwent dental extractions without interruption of their treatment, in order to analyze the incidence of postoperative bleeding according to the INR value. The 249 patients who underwent 543 dental extractions were divided into five groups: group 1 with INRs of 1.5–1.99, group 2 with INRs of 2–2.49, group 3 with INRs of 2.5–2.99, group 4 with INRs of 3–3.49, and group 5 with INRs >3.5. Of the 249 patients, 30 presented with postoperative bleeding (12%): group 1, three patients presented with bleeding (5%); group 2, 10 patients (12.8%); group 3, nine patients (15.2%); group 4, five patients (16.6%); and group 5, three patients (13%). The incidence of postoperative bleeding was not significantly different among the five groups. Al-Mubarak et al. (15) examined the consequences of the temporary withdrawal of warfarin and/or suturing on bleeding and healing patterns following dental extractions. Two hundred and fourteen patients on long-term oral warfarin therapy scheduled for dental extraction were randomly divided into four groups: no suturing and discontinued (group 1) or continued warfarin (group 2), and suturing and discontinued (group 3) or continued warfarin (group 4). Discontinuing warfarin reduced INR levels significantly at day 1, which subsequently reached <1.5 in 96 out of 104 patients (group 1 and 3). Statistical comparisons among the different treatment groups did not reveal any significant difference regarding bleeding status or healing pattern.

In all the above-mentioned studies, the course of postoperative bleeding was determined after the application of local hemostatic agents. However, in the study of Karslı et al. (8), the amount of blood loss during the first 20 min after extraction was estimated before packing the extraction socket with oxycellulose and then the direct effects of different anticoagulation treatments on patients' bleeding patterns could be evaluated. They assessed the safety of dental extraction without altering the warfarin regimen in patients with an INR from 1 to 4. Forty patients who underwent tooth extraction were divided into 4 groups: continuation of warfarin without interruption (group 1), warfarin bridged with LMWH (group 2), warfarin bridged with unfractionated heparin (group 3), and a control group of healthy individuals (group 4). The mean AOBs were 2.486±1.408, 999±425, 1.288±982, and 1.736±876 mg for groups 1, 2, 3, and 4, respec-

tively. There was no severe postoperative bleeding in any patient and the number of used extra gauze swabs did not differ significantly among the groups.

Similar to the study of Karslı et al. (8), the AOBs were measured with quantitative methods in our study. In addition, the data of the same patient in different dental extraction appointments were compared, eliminating the bleeding diathesis differences of patients. We think that these aspects show our study's merits above previous studies in the literature. The median number of used extra gauze swabs, the median bleeding time and the AOBs were all higher in the second dental extraction procedure group ($p<0.001$). There was a moderate correlation between INR values and the amount of bleeding in the patients under warfarin therapy ($r=0.41$, $p=0.01$). It is also necessary to point out that none of the patients receiving LMWHs had thromboembolic complications a month after the procedures.

In a recent study by BRUISE, investigators (16) showed that heparin-bridging therapy increased the frequency of hematoma formation compared with continuous warfarin therapy in patients who had undergone pacemaker implantation. Taking this result into account with our findings, we think that randomized controlled studies should be conducted to compare uninterrupted warfarin therapy with heparin-bridging therapy in patients undergoing moderate and major surgical procedures. It is obvious that surgery under continuous warfarin therapy is much easier, practical, and cheaper.

Study limitations

This study presents some potential drawbacks and limitations: 1) it has a relatively small sample size; and 2) all the patients on bridging therapy received enoxaparin, and thus our conclusions may not be generalizable to other preparations of LMWHs.

Conclusion

In conclusion, our study confirms that dental extractions are safe in therapeutically anticoagulated patients and showed that the median number of used extra gauze swabs, the median bleeding time, and the AOBs were all higher in patients under LMWH (enoxaparin sodium, Clexane, Sanofi-Aventis) bridging therapy than in patients under uninterrupted warfarin therapy. The results of our study are consistent with guidelines recommendation. This study showed that the incidence of bleeding after dental extractions performed under bridging therapy is higher than that after extractions performed under warfarin therapy. Actually, there is a need for further randomized clinical trials comparing the two management strategies with respect to the severity of bleeding complications in all surgical interventions.

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